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Circadian rhythm orchestrates the cell cycle of rat renal epithelial cells: A novel mechanism to regulate the cell cycle

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The nephron is composed of various types of differentiated cells, each of which is located at the right place at the right time to exert its specific function. During nephrogenesis and physiologic turnover of cells in mature nephron, the cell cycle of differentiated cells and its stem/progenitor cells should be orchestrated, otherwise the morphologic and functional integrity of the kidney would be deranged. Based on this concept, we hypothesized that circadian rhythm, which is maintained by an intrinsic time-keeping system regulating behavior and physiologic functions of organisms, might organize the proliferation of cells in the kidney. In fact, daily administration of 5-bromo-2′-deoxyuridine (BrdU) to pup or adult Sprague-Dawley rats at a specific clock time revealed that renal tubular epithelial cells in cortical and corticomedullary segments of the nephron proliferated rapidly in a synchronized manner but cells in the rest of segments and glomeruli were quiescent or proliferate slowly without apparent synchronization. We confirmed that the activity of cell cycle-related protein molecules such as extracellular signal-regulated protein kinase (ERK)1 and 2 oscillated with a synchronized 24-hour cycle. Restricted daytime feeding, a well-established manipulation to dissociate the circadian clock of peripheral organs from that of suprachiasmatic nucleus (SCN) (the master clock of the body), clearly shifted the phase of the synchronized cell cycle. It means that the clock not in SCN but in the kidney somehow releases a cue for the growth of tubular epithelial cells at the specific segments. Generally, the existence and oscillating phase of the circadian clock can be perceived by the oscillating expression of clock genes such as *Per*1 and *Per*2. Because *Per*1 and *Per*2 existed throughout the nephron, including glomeruli and oscillated with a 24-hour cycle, it is intriguing that cells only in the limited area of the kidney proliferate in accordance with the circadian rhythm.

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Cardiac and renal cell lineage derived from stem cells: Implication for organ regeneration

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The use of embryonic stem cells to regenerate damaged organs is proposed as an exciting therapeutic alternative. Basement membranes are composed of large glycoproteins such as type IV collagen, laminin, heparin sulfate proteoglycan, and nidogen/entactin. In the recent years, tissue-specific variants/isoforms of type IV collagen, laminin, and others have been identified, leading to the proposal of a new concept that "not all basement membranes are created equal." This immediately raises the question as to the role of these specific basement membranes in the regulation of cellular behavior tailored to the need to a given tissue. In the laboratory we have now isolated several tissue specific basement membranes and performed in vitro self-assembly studies. Our laboratory is engaged in research to evaluate the role of matrix and basement membrane molecules in the culture and propagation of stem cells. In this presentation, we will discuss how stem cells can be used to generate cardiomyocytes and also renal epithelial cells. Additionally, the use of stem cells in the context of acute and chronic renal injury will be discussed.

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Growth factor enhancement of mammalian regeneration

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The remarkable potential of lower vertebrates to rebuild heart and skeletal muscle contrasts with relatively poor regenerative capacity in mammals, which may not retain a sufficiently robust progenitor cell population into adulthood. Regeneration of the mammalian myocardium is perhaps the most recalcitrant, having apparently lost the ability to activate localized dedifferentiation of postmitotic cells that accompanies heart regeneration in lower vertebrates. Myogenic progenitors were enhanced in regenerating transgenic mouse muscle expressing a local insulin-like growth factor-1 (mIGF-1) isoform, which maintains tissue integrity during exercise and aging, counters muscle decline in degenerative disease and cachexia, and enhances